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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,826	09/14/2005	Diego Walther	BB-123	3100

23557 7590 07/05/2007

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ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
07/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,826	WALTHER ET AL.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 24-28* is/are pending in the application.

4a) Of the above claim(s) *1,4-21,24 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/EP03/07744.

Claims 1-21 and 24-28 are currently pending.

The preliminary amendment filed on 12/4/2006, amending claims 1-3 and canceling claims 22-23 is acknowledged.

Applicant's election with traverse of Group II, Claims 2, 3 and 25-27, drawn to an isolated tryptophan hydroxylase polypeptide and SEQ ID NO: 2 in the response filed on 12/4/2006 is acknowledged.

The traversal is on the ground(s) that the Group drawn to polynucleotide and Group drawn to polypeptide should be examined together without substantial burden to the Office. This is not found persuasive because as described in the previous Office action, the polynucleotide encoding a polypeptide neuronal tryptophan hydroxylase of Group I and polypeptide neuronal tryptophan hydroxylase of Group II and antibody of Group III are each unrelated and chemically distinct entities. The only shared technical feature of these groups is that they all relate to polynucleotide encoding a polypeptide neuronal tryptophan hydroxylase. However, this shared technical feature is not a "special technical feature" as defined by PCT Rule 13.2 as it does not define a contribution over the art. According to the search report (PCT form 210), a DNA encoding a neuronal tryptophan hydroxylase polypeptide is known in the art (WO/2002/17891, see IDS). Thus, a neuronal tryptophan hydroxylase polypeptide does not make contribution over the prior art. Examining all the groups and all the DNAs and proteins sequences, which would include mutants and variants and searching DNA/protein sequence databases as well as searching non-patent literature, Patent and pending databases would impose a serious burden to the Office.

Applicants also argue that lack of unity does not exist and recited as evidence International search report (ISR). This is not persuasive because according to ISR the above reference discloses nucleic acid and polypeptide of the instant application and according to novelty and inventive state, the ISR clearly showed that the subject matter in Claims 1, 2, 4-7, 22 and 23 is not novel and none of the claims 1, 2, 4-7, 22 and 23 meets the requirements of Article 33(2) PCT. In addition, the above reference is documented as "X" reference in the ISR. Furthermore, Yu et al. (WO/02/97039-A2, publication 12/5/2002, claim priority of 60/294076 filed on 5/29/2001) teach a polypeptide, which is 100% identical to SEQ ID NO: 2 having tryptophan hydroxylase activity. Therefore, the polypeptide of the instant application does not make contribution as prior art and lacks unity of invention.

The requirement is still deemed proper and is therefore made **FINAL.**

Claims 1, 4-21, 24 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 2-3, and 25-27 are under consideration and are being examined herein.

Priority

Acknowledgement is made of applicants claim for foreign priority of application Germany 10232151.5 filed on 7/16/2002.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 12/6/2005 and 2/25/2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97.

Accordingly, the information disclosure statement is considered by the examiner. The signed copy of IDS is enclosed herewith.

Drawings

Drawings submitted on 12/30/2004 are objected by the Examiner for the recitation of the nucleic acid and protein sequences without appropriate sequence identifiers i.e. SEQ ID NOs. Examiner urges the applicants to provide sequence identifiers in response to this Office action. See particularly 37 CFR 1.821(d).

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

In this case abstract has three paragraphs. Appropriate corrections are required.

Claim Objections

Claim 2 is objected to as depending from non-elected claim i.e. claim 1. Applicants are advised to include the related limitations in the context of the elected polypeptide of claim 1 into claim 2. Appropriate correction is requested.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 2-3 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 2-3 recite "The polypeptide", which reads on a naturally occurring polypeptide. Naturally occurring polypeptide is not patentable.

In the absence of the hand of man, naturally occurring nucleic acids and /or proteins are considered non-statutory subject matter. *Diamond and Chakrabarty*, 206 USPQ 193 (1980). This rejection may be overcome by amending the claims to contain wording such as "An isolated polypeptide". For examination purpose the claim is read as such.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2-3 and 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2, which depends on claim 1, is indefinite in the recitation of "biological activity" as it is unclear what the scope of activities that is encompassed by this term includes. The specification does not define the term "biological activity", however, specification teaches that the polypeptide of SEQ ID NO: 2 have tryptophan hydroxylase activity. It is not clear to the examiner whether the term "biological activity" of said polypeptide means tryptophan hydroxylase activity or something else.

Claims 2-3 and 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2, which depends on claim 1, is indefinite in the recitation "activity of the polypeptide is not significantly reduced", wherein the phrase "not significantly reduced" is a relative term, which renders the claim indefinite. The phrase is not defined by specification and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. The claim should define and clearly state as to what the reduction of said polypeptide activity is being compared.

Claims 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim is indefinite as the recitation "in particular" renders the claim indefinite

because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 27 is indefinite in the recitation "the peripheral and neuronal serotonin production are simultaneously increased or decreased" renders the claim indefinite. The phrase is not defined clearly by the specification. The claim should define and clearly state as to what the increase or decrease of said polypeptides production are being compared. It is also unclear, how serotonin production is a property of the claimed composition.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 25-27 are directed to a combination therapeutic comprising any polypeptide of SEQ ID NO: 2 encoded by the nucleic acid sequence of SEQ ID NO: 1 having degenerated genetic code or any derivatives of a polypeptide encoded by SEQ ID NO: 1 or any polypeptide having 80% identity to a polypeptide encoded by SEQ ID NO: 1 or any polypeptide having TPH

activity exhibit polymorphisms and an additional protein involve in serotonin metabolism (claim 25) or an additional protein any peripheral tryptophan hydroxylase (claim 26), which is characterized in increased or decreased peripheral and neuronal serotonin production.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical*).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description (see *Enzo* paraphrase above).

Thus, Claims 25-27 are directed to a combination therapeutic comprising the polypeptide of SEQ ID NO: 2 and an additional protein, which is involve in serotonin metabolism, wherein said additional protein is any peripheral tryptophan hydroxylase, including mutants and variants. Claims are thus drawn to a combination therapeutic comprising the polypeptide of SEQ ID NO: 2 and an additional protein, wherein said additional protein is any peripheral tryptophan hydroxylase, wherein said protein structure is not fully described in the specification. No information, beyond the characterization of a protein having tryptophan hydroxylase activity in the peripheral region. The specification does not contain any disclosure of the structure of all the mutants or variants of any peripheral tryptophan hydroxylase used to make combination therapeutic in the claim. The genus of polypeptides used in making the therapeutic is a large variable genus including mutants and variants, which can have wide variety of structures. Therefore, many structurally unrelated polypeptides are encompassed within the scope of the claims. The specification discloses the structure of only a single representative species of the claimed genus, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 2 and 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 2 from human or a

combination therapeutic of the protein of SEQ ID NO: 2 with peripheral tryptophan hydroxylase of GenBank Accession No. P17752 from human, does not reasonably provide enablement for any tryptophan hydroxylase which is 80% identical to SEQ ID NO: 2 and a combination with thereof with any additional protein involve in serotonin metabolism (claim 25) from any source or an additional protein of any peripheral tryptophan hydroxylase (claim 26) from any source, which is characterized in increased or decreased peripheral and neuronal serotonin production. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands (858 F.2d 731,737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows:

(1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors, which have, lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed below:

The breath of the claims:

Claims 2 (depends on claim 1), 25 and 26 are so broad as to encompass any polypeptide which is 80% identical to SEQ ID NO: 2 and a combination therapeutic there of with any additional protein involve in serotonin metabolism (claim 25) from any source or an additional protein of any peripheral tryptophan hydroxylase (claim 26) from any source.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins involve in serotonin metabolism or peripheral and neuronal tryptophan hydroxylase including mutants and variants broadly encompassed by the claims. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one neuronal tryptophan hydroxylase protein i.e. SEQ ID NO: 2 used to make the therapeutic.

The amount of direction or guidance presented and the existence of working examples:

The specification discloses a human neuronal tryptophan hydroxylase of SEQ ID NO: 2 and combination therapeutics thereof with a tryptophan hydroxylase of the peripheral tissue, which is a variant of neuronal tryptophan hydroxylase involve in serotonin metabolism. However, the specification fails to provide any clue as to the structural elements required in any neuronal tryptophan hydroxylase, which is 80% identical to SEQ ID NO: 2 and any polypeptide involve in serotonin metabolism or any peripheral tryptophan hydroxylase proteins to be used in the claimed therapeutic, or which are the structural elements in said proteins to be used in the claimed therapeutic known in the art that are essential for successfully practice the claimed therapeutic. No correlation between structure and function has been presented.

The specification does not support the broad scope of the claims which encompass any neuronal tryptophan hydroxylase, which is 80% identical to SEQ ID NO: 2 and any polypeptide involve in serotonin metabolism or any peripheral tryptophan hydroxylase proteins to be used in the claimed therapeutic because the specification does **not** establish: (A) regions of the protein structure which may be modified without affecting tryptophan hydroxylase activity and; (B) the general tolerance of tryptophan hydroxylase polypeptide to modification and extent of such

tolerance; (C) a rational and predictable scheme for modifying any tryptophan hydroxylase polypeptide residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any polypeptide which is 80% identical to SEQ ID NO: 2 and any additional protein involve in serotonin metabolism (claim 25) from any source or an additional protein of any peripheral tryptophan hydroxylase (claim 26) from any source. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a combination therapeutic comprising any polypeptide which is 80% identical to SEQ ID NO: 2 and any additional protein involve in serotonin metabolism or any peripheral tryptophan hydroxylase having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art:

The amino acid sequence of a polypeptide determines its structural and functional properties. While the specification discloses a single human neuronal tryptophan hydroxylase protein, neither the specification nor the art provide a correlation between structure and function such that one of skill in the art can envision the structure of any neuronal tryptophan hydroxylase

protein and an additional any protein involve in serotonin metabolism or any peripheral tryptophan hydroxylase protein used to make the therapeutic. The art clearly teaches that modification of a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are tolerant of modification and which ones are conserved is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (1999) and Seffernick et al. (2001), where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required practicing the claimed invention based on the teachings of the specification:

While methods of generating or isolating variants of a polynucleotide were well known in the art at the time of invention, it is not routine in the art to screen by trial and error process for (1) all nucleic acids encoding any protein which is 80% identical to SEQ ID NO: 2, (2) an essentially infinite number of mutations of any gene encoding any tryptophan hydroxylase protein sequence. The amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such

modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification.

Conclusion:

Therefore, taking into consideration of the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al. (WO/2002/97039, publication 12/5/2002, claim priority of US application 60/294076, filed on 5/29/2001, see IDS). Instant claims drawn to an isolated polypeptide of SEQ ID NO: 2 having tryptophan hydroxylase activity and a therapeutic comprising said polypeptide and an additional

polypeptide serotonin metabolic activity.

Yu et al. teach a polypeptide having 100% identity to SEQ ID NO: 2 of the instant application as well as nucleotide sequence. Yu et al. also teach that said polypeptide is human tryptophan hydroxylase having tryptophan hydroxylase activity. Yu et al. further teach variants of said tryptophan hydroxylase having tryptophan hydroxylase activity. Furthermore, Yu et al. teach that said polypeptide could be used as pharmaceutical composition for therapeutic treatment related to anxiety, depression, hyperactivity or sleep disorder. Therefore, Yu et al. anticipate claim 2-3 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25-27 are rejected under 35 U.S.C. 103 (a) as being obvious over Yu et al. (WO/2002/97039, publication 12/5/2002, claim priority of US application 60/294076, filed on 5/29/2001, see IDS) as applied to claim 2-3 above in view of Wang et al. (J Neurochem. 1998 Oct; 71(4): 1769-72) and Veenestra-VanderWeele et al. (Knockout mouse points to second form of tryptophan hydroxylase, Mol Interv. 2003 Mar; 3(2): 72-5, 50. Review). Instant claims drawn to a therapeutic composition comprising an isolated polypeptide of SEQ ID NO: 2 having tryptophan hydroxylase activity and an additional polypeptide having serotonin metabolic activity.

Yu et al. teach a polypeptide having 100% identity to SEQ ID NO: 2 of the instant application as well as nucleotide sequence. Yu et al. also teach that said polypeptide is human tryptophan hydroxylase having tryptophan hydroxylase activity. Yu et al. further teach variants of said tryptophan hydroxylase having tryptophan hydroxylase activity. Furthermore, Yu et al. teach that said polypeptide could be used as pharmaceutical composition for therapeutic treatment related to anxiety, depression, hyperactivity or sleep disorder. Yu et al. do not teach a composition comprising said tryptophan hydroxylase protein and an additional peripheral tryptophan hydroxylase protein having serotonin metabolism activity.

Wang et al. teach [redacted] alternative splicing at the 3'-cDNA of human tryptophan hydroxylase, which give rise to two isoforms of human tryptophan hydroxylase i.e. one is short form TPH1 i.e. spliced (444 amino acids) and another is long form TPH2 i.e. un-spliced (490 amino acids), which is neuronal specific. Wang et al. do not clearly teach functional significance of these two isoforms.

However, Veenestra-VanderWeele et al. teach two isoform of TPH, specifically also neuronal specific TPH2 expression in brain. Veenestra-VanderWeele also teach by knockout inactivation of TPH1 (which is peripheral TPH) results in no serotonin production in the gut with no behavioral change but significant serotonin production in brain due to the presence of TPH2, which indicates that TPH2 (neuronal) is more potent than TPH1 in terms of serotonin metabolism.

Since, Yu et al. clearly teach said tryptophan hydroxylase, a serotonin metabolic enzyme and a composition comprising said protein for using as therapeutic, it would have been obvious to one to ordinary skill in the art at the time of the invention was made to make a therapeutic composition comprising said neuronal tryptophan hydroxylase protein and an additional splice variant of tryptophan hydroxylase of Wang et al. and Veneestra-VanderWheele et al. for increased serotonin production for a making a pharmaceutical composition for treating diseases like anxiety, depression, or sleep disorder.

One of ordinary skill in the art would have a reasonable expectation of success in making a therapeutic composition comprising the polypeptide of Yu et al. and adding another splice variant of tryptophan hydroxylase protein of Wang et al. to enhance the serotonin production for treating disease related to anxiety, depression, hyperactivity or sleep disorder.

One of ordinary skill in the art would have a reasonable expectation of success because Yu et al. suggested to make a composition comprising said protein could be used for therapeutic purpose.

Therefore, claims 25-27 would have been prima *facie* obvious to use of ordinary skill in the art.

Conclusion

Status of the claims:

Claims 1-21 and 24-28 are pending.

Claims 1, 4-21, 24 and 28 are withdrawn.

Claims 2-3 and 25-27 are rejected.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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